REMARKS

Claims 51-73 were pending in the above-identified application. By the amendment made herein, claims 72-73 were canceled, without prejudice to Applicant's right to pursue the subject matter of the canceled claims in other applications, claims 51, 55, 56, 60, 61, 69, 70, and 71 were amended, and claims 74-78 were added, to more particularly point out and distinctly claim the invention, and to correct for improper multiple claim dependencies. Thus, the objection to claims 72 and 73 for improper multiple claim dependencies has been obviated. These amendments and new claims are fully supported by the instant specification (see, *e.g.*, page 12, lines 19 to 28; page 78, line 29 to page 79, line 2; and, in general, Section 5.8), and, as such, do not represent new subject matter. A marked-up version of the claim amendments are attached hereto as Exhibit A, which indicates added matter by underlining and deleted matter by brackets.

The specification has been amended to conform the Abstract to a single paragraph and to correct informalities in the Table of Contents and the Brief Description of the Figures. A marked-up version of the amendments to the specification is attached hereto as Exhibit B, which indicates added matter by underlining and deleted matter by brackets.

Thus, claims 51-71 and 73-78 will be pending upon entry of the instant amendments. A copy of the pending claims upon entry of the amendments is attached hereto as Exhibit C. Applicant respectfully requests that the amendments and remarks presented herein be entered into the record of the instant application.

1. THE CLAIMED INVENTION

The present invention relates to methods for identifying molecules which modulate interaction between cell surface receptors and heat shock proteins (hsps), such as gp96, Hsp70 and Hsp90. The invention is based, in part, on the Applicant's discovery that heat shock proteins can bind to cell surface receptors, allowing the heat shock protein to be endocytosed into the cell. The receptor is associated with the cell membranes of macrophages, dendritic cells, and other cell types. The existence of such hsp receptors on the cell surface was unexpected because, at the time of filing of the instant application, hsps were known to be very abundant, intracellular proteins, making the existence of a specific cell surface receptor for hsps unlikely. The Applicant's discovery of such a cell surface heat shock protein receptor

involved in the binding of hsps or hsp-peptide complexes provides useful reagents and methods for identifying molecules which modulate immunity by hsp and hsp-peptide complexes.

2. THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

Claims 51-73 are rejected under 35 U.S.C. § 112, first paragraph, for lack of written description. In particular, the Examiner contends that, while the claims are drawn to methods for screening a molecule for the ability to modulate heat shock protein receptor activity, the claims "are genus claims encompassing any heat shock protein receptor from any organism that can display any type of receptor activity", and, as such, the written description is not commensurate in scope with the claims.

The legal standard for the written description requirement of 35 U.S.C. § 112, first paragraph, requires that an applicant "must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555; 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). The Federal Circuit has recently stated that the description is deemed sufficient if it demonstrates to the skilled artisan that the applicant was in possession of the necessary common attributes of the members of the genus. *Regents of the University of California v. Eli Lilly*, 119 F.3d at 1568.

The criteria for determining sufficiency of written description set forth in Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112 ¶ 1, "Written Description" Requirement" ("the Guidelines") (published in the January 5, 2001 Federal Register at Volume 66, Number 4, pages 1099-1111), specifies that an applicant may show that an invention is complete by "disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention." (*Id.* at page 1106, column 1, lines 22-33). According to the Guidelines, for each claimed genus, the test requires determination of whether there is sufficient description of

> " . . .a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, functional characteristics when coupled with known or disclosed correlation between function and structure, or some combination of such identifying characteristics sufficient to

show the applicant was in possession of the claimed genus." *Id.* at page 1106, column 3, lines 12-29.

Where the specification discloses any relevant identifying characteristics, *i.e.,* physical, chemical and/or functional characteristics, sufficient to allow a skilled artisan to recognize the applicant was in possession of the claimed invention, a rejection for lack of written description under Section 112, first paragraph, is misplaced.

In the instant action, the Examiner has applied the genus test, and contends that the specification does not disclose a sufficient number of heat shock receptors that would have described the representative species of all heat shock protein receptors. In particular, the Examiner contends that the disclosure of the three heat shock protein receptors is not deemed to be descriptive of the complete structure of a representative number of species encompassed by the claims, as one of skill in the art cannot envision the complete structure of any other heat shock protein receptor based on the disclosed heat shock protein receptors. The Examiner contends further that there is "no description of a representative number of species by partial structure and a function which correlates with a structure as there is no disclosure of the properties and/or characteristics that constitute a heat shock protein receptor." Additionally, the Examiner asserts, there is no description of the activities that specifically describe receptor activities. The Applicant respectfully disagrees, for the reasons set forth below.

The Applicant respectfully submit that the specification, as filed, provides written description support under the genus test for the claimed subject matter including the claimed screening methods. Contrary to the Examiner's contention, knowledge of the complete structure of a heat shock protein receptor is not part of, nor required for, the claimed invention. The claimed screening methods require heat shock protein receptor positive cells (hereinafter "hspr positive cells"), and the ability to assay for an activity of an hspr. Specifically, the first independent claim, claim 51, as amended, is drawn to a method for screening a molecule for the ability to modulate heat shock protein receptor activity comprising: (a) contacting hspr positive cells with the molecule; and comparing the level of hspr activity in cells contacted with the molecule to the amount of hspr activity in cells not so contacted. The second independent claim, claim 52, is drawn to a method for screening a molecule for activity to modulate, directly or indirectly, the ability of hspr positive cells to stimulate the activation of cytotoxic T cells *in vitro* comprising: adding the molecule to a mixture of heat shock protein receptor positive cells and cytotoxic T cells under conditions conducive to the activation of cytotoxic T cells; and comparing antigenic cell cytotoxicity of said T cells with the

cytotoxicity of T cells that are formed in the absence of said molecule.

Hspr positive cells are characterized, both structurally as well as functionally, in the instant application. In particular, the detection, purification, and isolation of hsp70 receptor positive cells, hsp90 receptor positive cells, and gp96 receptor positive cells from particular cell types, such as macrophages and/or dendritic cells, is described in the application as originally filed (see, for example, page 15, line 11, to page 28, line 24). Furthermore, the isolation, purification, and characterization of gp96 receptor positive cells is provided in a working example (page 109, line 1 to page 112, line 27; Figures 1-5). In addition, contrary to the Examiner's contention, hspr positive cells are also functionally described in the specification. Numerous heat shock protein receptor assays are disclosed which measure the activity of hspr positive cells, such as, for example, binding assays, including but not limited to, direct binding assays (see, for example, page 74, lines 12 - 24, and Section 5.8, in particular, page 78, line 29 to page 79, line 2), competition hsp binding assays or antibody assays (see, for example, page 74, lines 12 - 24, and Section 5.9, in particular, page 80, line 21 to page 81, line 16), and T-cell acytotoxicity assays to test for the hspr mediated activation of cytotoxic T cells (page 73, line 13 to 22).

In light of the legal standard discussed *supra*, Applicant submits that sufficient representative members of the genus are taught to allow the skilled artisan to "visualize or recognize the identity of the members of the genus." As acknowledged by the Examiner, the "..specification disclosed three heat shock protein receptors: a receptor that binds hsp70, a receptor that binds hsp90, an a receptor that binds gp96." According to the Examiner, however, the specification does not describe how to identify other receptors for other heat shock protein in any other organism. Furthermore, the Examiner contends that it is unclear from which species the claimed heat shock protein receptors have been derived, and the specification fails to teach how to identify the receptors for heat shock proteins other than the murine gp96 set forth in the example (pages 109-116). The Applicant respectfully disagrees with both contentions, for the following reasons.

Applicant asserts that the application provides general teaching and description for how to identify an hspr positive cell corresponding to any heat shock protein in any organism. Using the methods taught in the application, as well as standard techniques known in the art, hspr positive cells (see, for example, Section 5.1 and 5.2, in particular, page 24, line 31, to page 28, line 24) may be isolated from particular cell types, such as macrophages and/or dendritic cells, by their ability to interact with hsps or hsp-peptide complexes. Because heat

shock proteins are highly conserved across a diversity of organisms (see page 3, lines 3 to 15), the disclosed methods provide general teaching for purification of hsps and hsp-complexes, applicable for isolating hspr positive cells from a wide variety of sources (see, for example, page 16, line 6, to page 18, line 5).

The Examiner further argues that " . . it is unclear if one heat shock protein receptor binds the three disclosed heat shock proteins (hsp70, hsp90, and gp96), or if there are three distinct heat shock protein receptors." Applicant submits, however, that the claimed methods do not require any such distinction, because the claimed methods work whether the hsp receptor positive cell binds to one, or more than one, hsp. In fact, both types of receptors have been isolated. For example, CD91, an hspr expressed on macrophages and dendritic cells binds several hsps, including gp96, hsp70, Hsp90, and calreticulin (Binder et al., 2000, Nat Immunol.1:151-5, which is attached hereto as Exhibit E; and Basu et al., 2001, Immunity 14: 303-313, which is attached hereto as Exhibit F). On the other hand, another recently identified hspr, CD36, is also expressed on macrophages and dendritic cells, binds gp96 (Panjwani et al., 2001, Abstract presented at 11th International Congress of Immunology, Stockholm, which is attached hereto as Exhibit G; and Panjwani et al., 2000, Abstract presented at the II International Conference Heat Shock Proteins in Immune Response, Farmington, Connecticut, which is attached hereto as Exhibit H), but does not bind either hsp70 or hsp90. Despite this distinction, both types of receptors and hspr positive cells are useful in the claimed screening methods, demonstrating that whether a particular hspr positive cell binds to one, two, or many hsps, is immaterial to the use of the hspr positive cells in the claimed invention.

In view of the foregoing, Applicant respectfully maintains that the rejection of claims 51-73 under 35 U.S.C. § 112, first paragraph, for lack of written description is improper and request that the rejection be withdrawn.

3. THE REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN

Claims 51 and 53-73 are rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. In particular, the Examiner contends that it is not clear what activities specifically constitute "receptor activity". In response, Claim 51 has been amended to recite the hsp receptor activity is receptor binding activity. Receptor binding activity, *i.e.*, binding of hsps or other ligands by the receptor, is clearly defined, and numerous such receptor binding assays are provided, throughout the application (see, for example, page 12, lines 19 to 28; page

line 29 to page 79, line 2; and, in general, Section 5.8).

In addition, Claim 55 is further rejected for failing to provide antecedent basis for "heat shock protein receptor positive cells". In response, claim 51 has been amended to recite heat shock protein receptor positive cells, providing the requisite antecedent basis.

In view of the foregoing, Applicant respectfully maintains that the rejections of claims 51 and 53-73 under 35 U.S.C. § 112, second paragraph, have been obviated, and request their withdrawal.

CONCLUSIONS

Entry of the foregoing amendments and remarks into the record of the above-identified application is respectfully requested. Withdrawal of all rejections and reconsideration of the amended claims are requested. An early allowance is earnestly sought.

Please charge the required fee to Pennie & Edmonds LLP Deposit Account No. 16-1150.

Respectfully submitted,

Date: December 5, 2001

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Enclosures

EXHIBIT A:
MARKED-UP VERSION OF THE CLAIM AMENDMENTS

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51. (amended) A method for screening a molecule for the ability to modulate heat shock protein receptor activity comprising:

(a) contacting heat shock receptor positive cells with the molecule; and

(b) comparing the level of heat shock protein receptor binding activity in the heat shock receptor positive cells contacted with the molecule to the amount of heat shock protein receptor binding activity in the heat shock receptor positive cells not so contacted,

wherein an increase or decrease in the amount of heat shock protein receptor binding activity in the contacted heat shock receptor positive cells relative to the amount of heat shock protein receptor binding activity in the heat shock receptor positive cells not so contacted indicates that the molecule has the ability to modulate heat shock protein receptor activity.

55. (amended) The method of claim 51 wherein the level of heat shock protein receptor binding activity is assayed by measuring the ability of the molecule to bind to the heat shock protein receptor positive cells.

56. (amended) The method of claim 51 wherein the level of heat shock protein receptor binding activity is assayed by measuring the ability of the molecule to modulate the binding of a heat shock protein or a heat shock protein-peptide complex to the cells.

60. (amended) The method of claim 51 wherein the heat shock protein receptor binding activity is the ability to interact with a heat shock protein receptor antibody.

61. (amended) The method of claim 51 wherein the level of heat shock protein receptor binding activity is assayed by measuring antigen presentation.

69. (amended) A method for identifying a molecule useful for the treatment of cancer comprising carrying out the method of claim 51[or 52], further comprising the step of administering the molecule to a non-human animal, and determining whether the molecule

alters tumor progression in the treated animal.

70. (amended) A method for identifying a molecule useful for the treatment of an infectious disease comprising carrying out the method of claim 51[or 52], further comprising the step of administering the molecule to a non-human animal, and determining whether the molecule ameliorates the infectious disease in the treated animal.

71. (amended) A method for identifying a molecule useful for the treatment of an autoimmune disease comprising carrying out the method of claim 51[or 52], further comprising the step of administering the molecule to a non-human animal, and determining whether the molecule ameliorates the autoimmune disease in the treated animal.

74. (new) A method for identifying a molecule useful for the treatment of cancer comprising carrying out the method of claim 52, further comprising the step of administering the molecule to a non-human animal, and determining whether the molecule alters tumor progression in the treated animal.

75. (new) A method for identifying a molecule useful for the treatment of an infectious disease comprising carrying out the method of claim 52, further comprising the step of administering the molecule to a non-human animal, and determining whether the molecule ameliorates the infectious disease in the treated animal.

76. (new) A method for identifying a molecule useful for the treatment of an autoimmune disease comprising carrying out the method of claim 52, further comprising the step of administering the molecule to a non-human animal, and determining whether the molecule ameliorates the autoimmune disease in the treated animal.

77. (new) The method of claim 51, 52, 69, 70, 71, 74, 75, or 76, wherein the heat shock protein receptor is selected from the group consisting of an Hsp70 receptor, an Hsp 90 receptor, and a gp96 receptor.

78. (new) The method of claim 51, 52, 69, 70, 71, 74, 75, or 76, wherein the heat shock protein receptor positive cells are purified from heat shock protein receptor negative cells.

PURIFICATION OF HEAT SHOCK/STRESS PROTEIN CELL SURFACE RECEPTORS AND THEIR USE AS IMMUNOTHERAPEUTIC AGENTS

4. Brief Description Of The Figures

Figure 1A-[C]1E. gp96 receptor positive cells. A) Light microscopy[(left panel)], or B) confocal microscopy [(right panel)] of gp96 bound to membranes of peritoneal cells of C57/BL6 mice. [A]C) Negative control, unlabel[l]ed. [B]D) Negative control, label[l]ed with BSA-biotin. [C]E) gp96-biotin label[l]ed.

Figure 2A-2C. Time course of gp96-biotin internalization by peritoneal cells of C57/BL6 mice. A) Top left panel, light microscopy of a peritoneal cell, followed by confocal microscopy of a time course of gp96-biotin uptake by the same cell at 37°C, shown after 0, 2, 4, 6, 8, 10, 12, or 14 mins. B) Left panel, light microscopy of a peritoneal cell, followed by a confocal microscopy time course of gp96-biotin uptake by the same cell at 4°C, label[l]ed for 0, and 120 mins.

Figure 3A-3C. gp96 receptor positive cells. A)Light microscopy[(left panel)], or B) confocal microscopy[(right panel)] of gp96 bound to membranes of peritoneal cells of the transgenic mouse ImmortoMouse. [A]D) Negative control, unlabel[l]ed. [B]E) Negative control, label[l]ed with BSA-biotin. [C]F) gp96-biotin label[l]ed.

Figure 4. FacScan analysis of Hsp90 (column 1), gp96 (column 2), Hsp70 (column 3), and BSA (column 4) label[l]ed with FITC and pulsed on to Mac-1 positive cells (macrophage) at HSP concentrations of 10 μg/ml (row 1), 20 μg/ml (row 2), 50 μg/ml (row 3), 100 μg/ml (row 4), and 190 μg/ml (row 5). X axis measures FITC absorb[a]ence; Y axis measures propidium iodine (PI) absorb[a]ence.

Figure 5. HSP Receptor saturation by ^{125}I-label[l]ed gp96 in

BALB/C Mac-1+ cells and C57BL/6 Mac-1+ (macrophage) cells. ^{125}I-label[l]ed BSA is shown as a negative control.

ABSTRACT

The present invention relates to receptors for heat shock proteins (HSPs), such as gp96, Hsp70 and Hsp90. The receptor is associated with the cell membranes of a subset of antigen presenting cells, such as macrophages, dendritic cells. [

]The invention provides methods for identifying and isolating cells that express the heat shock protein receptor, the heat shock protein receptor, antibodies to heat shock protein receptor and nucleic acid molecules encoding heat shock protein receptor, and fragments thereof. The present invention further provides methods of use of the heat shock protein receptor positive cells, heat shock protein receptor protein, heat shock protein receptor antibodies, and heat shock protein receptor genes in methods for screening a molecule for the ability to modulate heat shock protein levels or activities. [Methods for identifying a molecule that enhance or block the function of heat shock protein receptor are included in the invention. The compositions of the invention may be used in various diagnostic and therapeutic applications in the area of cancer and infectious diseases.]

51. A method for screening a molecule for the ability to modulate heat shock protein receptor activity comprising:

(a) contacting heat shock receptor positive cells with the molecule; and

(b) comparing the level of heat shock protein receptor binding activity in the heat shock receptor positive cells contacted with the molecule to the amount of heat shock protein receptor binding activity in the heat shock receptor positive cells not so contacted,

wherein an increase or decrease in the amount of heat shock protein receptor binding activity in the contacted heat shock receptor positive cells relative to the amount of heat shock protein receptor binding activity in the heat shock receptor positive cells not so contacted indicates that the molecule has the ability to modulate heat shock protein receptor activity.

52. A method for screening a molecule for activity to modulate, directly or indirectly, the ability of heat shock receptor positive cells to stimulate the activation of cytotoxic T cells *in vitro* comprising:

(a) adding the molecule to a mixture of heat shock protein receptor positive cells and cytotoxic T cells under conditions conducive to the activation of cytotoxic T cells; and

(b) comparing antigenic cell cytotoxicity of said T cells with the cytotoxicity of T cells that are formed in the absence of said molecule,

wherein a lower or higher degree of cytotoxicity indicates that the molecule modulates the activation of cytotoxic T cells.

53. The method of claim 51 wherein the cells are heat shock protein receptor positive cells.

54. The method of claim 52 or 53 wherein the heat shock protein receptor positive cells are macrophage or dendritic cells.

55. The method of claim 51 wherein the level of heat shock protein receptor binding activity is assayed by measuring the ability of the molecule to bind to the heat shock protein receptor positive cells.

56. The method of claim 51 wherein the level of heat shock protein receptor binding activity is assayed by measuring the ability of the molecule to modulate the binding of a heat shock protein or a heat shock protein-peptide complex to the cells.

57. The method of claim 56 wherein the molecule increases the binding of the heat shock protein or the heat shock protein-peptide complex to the cells.

58. The method of claim 56 wherein the molecule decreases the binding of the heat shock protein or the heat shock protein-peptide complex to the cells.

59. The method of any one of claims 56 to 58 wherein the heat shock protein is an Hsp70, an Hsp 90, or gp96.

60. The method of claim 51 wherein the heat shock protein receptor binding activity is the ability to interact with a heat shock protein receptor antibody.

61. The method of claim 51 wherein the level of heat shock protein receptor binding activity is assayed by measuring antigen presentation.

62. The method of claim 61 wherein measuring antigen presentation is carried out by measuring representation of a peptide by an MHC molecule.

63. The method of claim 51 or 52 wherein the molecule is a peptide or protein, or derivative, analog or fragment thereof.

64. The method of claim 63 wherein the peptide is a member of a peptide library.

65. The method of claim 51 or 52 wherein the molecule is a small organic molecule, a nonpeptide, or an antibody.

66. The method of claim 65 wherein the nonpeptide is a member of a nonpeptide library.

67. The method of claim 66 wherein the small organic molecule is a member of a small molecule library.

68. The method of claim 51 or 52 wherein the molecule is attached to a solid surface.

69. A method for identifying a molecule useful for the treatment of cancer comprising carrying out the method of claim 51, further comprising the step of administering the molecule to a non-human animal, and determining whether the molecule alters tumor progression in the treated animal.

70. A method for identifying a molecule useful for the treatment of an infectious disease comprising carrying out the method of claim 51, further comprising the step of administering the molecule to a non-human animal, and determining whether the molecule ameliorates the infectious disease in the treated animal.

71. A method for identifying a molecule useful for the treatment of an autoimmune disease comprising carrying out the method of claim 51, further comprising the step of administering the molecule to a non-human animal, and determining whether the molecule ameliorates the autoimmune disease in the treated animal.

74. A method for identifying a molecule useful for the treatment of cancer comprising carrying out the method of claim 52, further comprising the step of administering the molecule to a non-human animal, and determining whether the molecule alters tumor progression in the treated animal.

75. A method for identifying a molecule useful for the treatment of an infectious disease comprising carrying out the method of claim 52, further comprising the step of administering the molecule to a non-human animal, and determining whether the molecule ameliorates the infectious disease in the treated animal.

76. A method for identifying a molecule useful for the treatment of an autoimmune disease

comprising carrying out the method of claim 52, further comprising the step of administering the molecule to a non-human animal, and determining whether the molecule ameliorates the autoimmune disease in the treated animal.

77. The method of claim 51, 52, 69, 70, 71, 74, 75, or 76, wherein the heat shock protein receptor is selected from the group consisting of an Hsp70 receptor, an Hsp 90 receptor, and a gp96 receptor.

78. The method of claim 51, 52, 69, 70, 71, 74, 75, or 76, wherein the heat shock protein receptor positive cells are purified from heat shock protein receptor negative cells.